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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,731	04/25/2001	John Smit	08106-004001	7587

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Y Rocky Tsao
Fish & Richardson
225 Franklin Street
Boston, MA 02110-2804

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,731	SMIT, JOHN	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9,13,16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

Claims 1-8 are pending in the application.

Applicants' election without traverse of Group I, claims 1-6, in Paper No. 15, filed 11/13/02, is acknowledged.

Claims 7 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Receipt of Information Disclosure Statements filed as Paper Nos. 9, 13, and 16 are acknowledged.

Claim Objections

[1] Claim 2 is objected to because of the following informalities: the terms "a aspartate-proline" and "adjacent a junction" are grammatically incorrect and should be replaced with, for example, "an aspartate-proline" and "adjacent to a junction". Appropriate correction is required.

[2] Claims 5 and 6 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim shall not depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[3] Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (claims 2-4 dependent therefrom) are unclear in the recitation of "an acid solution with a strength insufficient to solubilize the fusion protein". From the claim, it would appear the expressed

fusion protein is insoluble. However, Smit et al. (US Patent 5,976,864; IDS reference AA of Paper No. 13) teach that a fusion protein comprising amino acids 944-1026 of a Caulobacter crescentus S-layer protein fused to heterologous polypeptides did not precipitate when expressed (column 17, lines 19-21). Smit et al. Teach that amino acids 944-1026 are sufficient for Caulobacter secretion (column 17). Therefore, based on the prior art, it is unclear as to whether a heterologous protein fused to any part of a Caulobacter S-layer protein C-terminal secretion signal will necessarily be insoluble. For purposes of examination, the examiner has interpreted the claim as meaning a method of cleaving an insoluble fusion protein. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[4] Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cleaving an insoluble fusion protein, wherein the insoluble fusion protein includes a first component comprising at least amino acids 905-1026 of the Caulobacter crescentus S-layer protein of SEQ ID NO:5 and a second component heterologous to Caulobacter, the insoluble fusion protein containing at least an aspartate-proline dipeptide, wherein the method comprises combining the insoluble fusion protein with an acid labile solution of a strength insufficient to solubilize the fusion protein for a time sufficient to cleave the fusion protein at the aspartate-proline dipeptide, does not reasonably provide enablement for a method of cleaving an insoluble fusion protein, wherein the insoluble fusion protein includes a first component that comprises any part of any Caulobacter S-layer protein including Caulobacter C-terminal secretion signal and a second component heterologous to Caulobacter, the insoluble fusion protein containing at least an aspartate-proline dipeptide, wherein the method comprises combining the insoluble fusion protein with an acid labile solution of a strength

insufficient to solubilize the fusion protein for a time sufficient to cleave the fusion protein at the aspartate-proline dipeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The specification teaches that due to sequences within the S-layer, the S-layer proteins are able to form insoluble aggregrates in culture medium (page 4, lines 10-12). However, it is known in the art that not all portions of the Caulobacter crescentus S-layer secretion signal are able to form insoluble aggregrates. Smit et al. (US Patent 5,976,864; IDS reference AA of Paper No. 13) teach that the transporter signal for secretion from Caulobacter is located in amino acids 944-1026 (column 17, lines 17-19). Smit et al. teach a fusion protein comprising amino acids 944-1026 of a Caulobacter crescentus S-layer protein fused to heterologous polypeptides was expressed and secreted by Caulobacter, but did not precipitate (column 17, lines 19-21). Smit et al. teach that the fusion protein precipitated when amino acids 905-1026 were included (column 17, 21 and 22). Based on the teachings of Smit et al., a skilled artisan would not expect *any* part of a Caulobacter C-terminal secretion signal to provide for an insoluble fusion protein, and would recognize that the art has demonstrated that at least amino acids 905-1026 are required for insolubility. Furthermore, neither the specification nor the prior art provides any guidance as to which of the amino acids of other S-layer proteins from other species of Caulobacter are required for secretion that impart insolubility on a fusion protein. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is

unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[5] Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smit et al. (US Patent 5,976,864; IDS reference AA of Paper No. 13; hereafter referred to as "Smit") in view of Ausubel et al. (*Current Protocols in Molecular Biology*, John Wiley and Sons, Inc., 1994; IDS reference AR of Paper No. 16; hereafter referred to as "Ausubel") and Better (US Patent 5,851,802). Claim 1 is drawn to a method of cleaving a fusion protein, wherein the fusion protein includes a first component that comprises all or part of a Caulobacter S-layer protein including a Caulobacter C-terminal secretion signal and a second component heterologous to Caulobacter, the fusion protein containing at least aspartate-proline dipeptide, wherein the method comprises combining a fusion protein with an acid labile solution of a strength insufficient to solubilize the protein for a time sufficient to cleave the fusion protein at the aspartate-proline dipeptide. Claim 2 limits the location of the aspartate-proline dipeptide of the fusion protein of the method of claim 1. Claims 3 and 4 limit the pH of the method of claim 1.

Smit teaches DNA constructs for expression and secretion of a Caulobacter crescentus S-layer protein (referred to as rsaA protein in Smit) fused to a heterologous protein (abstract). Smit teaches numerous advantages of generating a fusion protein using a Caulobacter S-layer protein-fusion over existing fusion protein expression systems including the ubiquitous and non-pathogenic nature of Caulobacter and relatively high protein expression levels (column 2). Smit teaches methods for creating expression vectors encoding a Caulobacter S-layer fusion protein and using said vectors for expression

and secretion of fusion proteins (Examples 1-8). Smit does not teach a method of cleaving the fusion protein under acidic conditions.

At the time of the invention, acid hydrolysis of a fusion protein at an aspartyl-prolyl (Asp-Pro) bond was well known in the prior art. For example, Ausubel teaches guidelines for cleavage of fusion proteins by hydrolysis at low pH (pages 16.4.13-16.4.14). Ausubel teaches this method should be conducted at an elevated temperature under acidic conditions to cleave an Asp-Pro bond (page 16.4.13). Ausubel suggests the presence of an Asp-Pro bond between the component domains (page 16.4.13). Ausubel teaches that it is often advantageous to remove a carrier protein moiety from the protein of interest in order to do biochemical and functional analyses (page 16.4.2).

At the time of the invention, the ability to cleave an insoluble fusion protein by acid hydrolysis at an Asp-Pro bond was known in the art. For example, Better teaches acid cleavage of a human osteogenic protein subunit D (Bone D) polypeptide-bacterial/permeability-increasing protein (BPI) fusion at an Asp-Pro bond by acid hydrolysis using a variety of pHs and elevated temperatures (columns 19 and 20). The Bone D-BPI fusion was expressed in E. coli, resulting in the formation of inclusion bodies (column 18). Better teaches the fusion protein treated at acidic pH and elevated temperature remained insoluble, providing a facile method of purification of the cleaved product (column 19).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Smit, Ausubel, and Better for a method of cleaving a Caulobacter S-layer protein fused to a heterologous protein using acidic conditions to cleave an Asp-Pro bond between the component domains. One would have been motivated for a method of cleavage of a Caulobacter S-layer protein fused to a heterologous protein using acidic conditions to cleave an Asp-Pro bond between the component domains in order to remove the Caulobacter S-layer protein to facilitate biochemical and functional characterization of a heterologous protein as taught by Ausubel as described above. One would have a reasonable expectation of success for a method for cleaving a Caulobacter S-layer protein fused to a heterologous protein using acidic conditions to cleave an Asp-Pro bond between the component domains

because of the results of Smit, Ausubel, and Better. Therefore, claims 1-6, drawn to a method for cleaving a fusion protein as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[6] Claims 1-4 are rejected.

[7] Claims 5 and 6 are objected to.

[8] No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~
1600